MEDICAL STAFF CONFERENCE

Thyrotoxicosis and Pregnancy

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SMITH:* This morning we are not going to talk about the medical condition of pregnancy per se, but about one of the possible complications, hyperthyroidism. Dr. Fitzgerald will present the case summary.

DR. FITZGERALD:† This was the first University of California admission for this 22-year-old white primagravida whose chief complaint was "thyroid trouble." She had been entirely well until March of this year, when she noticed a slight dysphagia for solids and liquids. The last normal menstrual period occurred in June. In July she noticed the gradual and progressive onset of increasing appetite, vomiting (which began as morning sickness, but which eventually occurred intermittently throughout the day), diarrhea, diaphoresis, anxiety, heat intolerance, diffuse muscle aches and wasting, and tachycardia with palpitations. She experienced an episode of blurred vision. She had recorded a 35-pound weight loss over the preceding seven months, despite increased appetite. In July the patient's physician told her that she had "big eyes." He obtained serum tests which showed increased thyroid function and confirmed her pregnancy with a urine study. The patient's past medical history and social history were noncontributory. Her family history was of interest in that one sister may be diabetic.

On initial examination the patient was thin and tremulous. The vital signs showed a pulse of 100 per minute with frequent extrasystoles, blood pressure within normal limits, respirations 16 per minute, temperature was 37°C (98.6°F). The skin was dry but there was no pretibial myxedema. Scattered spider angiomata were observed. Examination of the eyes revealed a prominent stare, lid lag, and mild exophthalmos. The patient was unable to wrinkle the forehead by elevation of the eyebrows. Extraocular movements and results of funduscopic examination were all within normal limits.

Examination of the neck revealed an enlarged thyroid gland weighing approximately 100 grams. The gland was tender and firm with a palpable systolic thrill and bruit. The chest was clear. The heart was not enlarged, but the point of maximum impulse was prominent and the rhythm was irregular with frequent extrasystoles and sinus tachycardia. There was a soft S_3 gallop at the apex and a 2/6 soft ejection murmur heard best at the pulmonic area. There was no hepatosplenomegaly. The uterus was firm with the fundus palpable at the symphysis pubis. The muscle mass in the extremities was decreased and there was generalized muscle weakness which was greater proximally than distally. Neurologic examination was normal save for a fine tremor and symmetrically increased deep tendon reflexes.

Initial laboratory studies showed a hematocrit of 37 percent with a white blood count of 5,500

*Lloyd H. Smith, M.D., Professor and Chairman, Department of Medicine.

†Faith Fitzgerald, M.D., Intern in Medicine.

per cu mm and a predominance of neutrophils in the differential. Urinalysis was normal. Electrolytes, creatinine, blood urea nitrogen, bilirubin, and alkaline phosphatase were all normal. The cholesterol was 136 mg per 100 ml. The initial true thyroxin (TT_4) was 23.2 micrograms per 100 ml (normal range, 3.0 to 7.5 micrograms per 100 ml) with a triiodothyronine (T_3) uptake of 52 percent (normal range, 25 to 35 percent). The urine pregnancy test was positive. Electrocardiogram showed a sinus tachycardia with frequent premature atrial contractions, ST segment elevation, and terminal T wave inversion in leads II, III, AVF, and V_2 through V_6.

On admission to hospital, treatment was begun with propylthiouracil, 800 mg per day in divided doses. Phenobarbital and propranolol, 40 mg per day in divided doses, were also given. Since the patient slept with the eyelids open, eye shields were provided for the exposure keratitis.

As thyroid function decreased, the dose of propylthiouracil was decreased. Rapid control of the premature atrial contractions allowed the discontinuation of the propranolol. There was, however, no clinical decrease in size of the thyroid or disappearance of the bruit and thrill during the stay in hospital.

At the time of leaving hospital the TT_4 was 11.2 micrograms per 100 ml and the T_3 uptake was 36 percent. Medications included propylthiouracil, 100 mg three times daily, and phenobarbital, 15 mg three times daily. Our plan was to recommend subtotal thyroidectomy in the middle trimester of pregnancy.

DR. SMITH: Thank you very much, Dr. Fitzgerald. We would like to call on Dr. Francis Greenspan to discuss this patient and this particular problem. I would like to ask Dr. Greenspan, is there an increased incidence of Graves' disease during pregnancy? What are the problems which occur in the diagnosis of hyperthyroidism in the presence of endocrine abnormalities of pregnancy? How do these abnormalities alter one's therapeutic approach?

DR. GREENSPAN:* Thyrotoxicosis and pregnancy are a relatively rare combination. At the University of California San Francisco from 1964 to 1968, we had approximately 10,000 deliveries and only eight pregnancies accompanied by thyrotoxicosis, an incidence of about 0.08 percent. Becker and Sudduth[1] found 30 patients with thyrotoxicosis in a review of about 150,000 pregnancies, an incidence of 0.02 percent. In their review of the literature (until 1959) they reported that the incidence ranged from 0.02 to 3.7 percent and averaged about 0.2 percent. The important point is that this is a relatively rare combination. The reason it is rare is that patients with thyrotoxicosis are usually relatively infertile. The two most common clinical situations are (1) thyrotoxicosis may antedate pregnancy, be brought under control with medication, and then pregnancy occur in a partially treated patient and (2) thyrotoxicosis may develop after the onset of a normal pregnancy. The patient under discussion, however, became pregnant very early in the course of the thyrotoxicosis, so that both developed almost simultaneously.

*Francis S. Greenspan, M.D., Clinical Professor of Medicine.

Diagnosis of Thyrotoxicosis During Pregnancy

Clinical Findings: The recognition of thyrotoxicosis during pregnancy may be very difficult. The normal pregnant patient may complain of excessive warmth and nervousness. She may have signs of tachycardia, tremor, and some slight thyroid enlargement. The clinical signs that suggest thyrotoxicosis are the presence of eye signs, such as lid lag, lid retraction, stare, and exophthalmos. A bruit heard over the thyroid gland is very suggestive. Finally, the occurrence of weight loss despite a good appetite is a characteristic clinical sign. Many patients lose weight early in the pregnancy because of "morning sickness," but this weight loss is obviously associated with poor appetite. When a patient either loses weight or fails to gain weight despite a good caloric intake, one must suspect the presence of thyrotoxicosis.

Laboratory Tests: The diagnosis of thyrotoxicosis in pregnancy can easily be made on the basis of commonly available laboratory studies, but it is important to recognize that many of these tests have a different range for the normal pregnant female than for the nonpregnant female. A summary of the tests of thyroid function in pregnancy is presented in Table 1.

In 1951, Dr. Evelyn Man[2] presented data on the serum precipitable iodine in the course of normal pregnancy. She showed a striking rise in the serum precipitable iodine or the protein-bound iodine (PBI) occurring about the fourth week in

TABLE 1.—*Tests of Thyroid Function in Women*

Test	Normal Nonpregnant	Normal Pregnant	Hyperthyroid Pregnant
Protein-Bound Iodine (micrograms per 100 ml)	4.0 to 8.0	6.0 to 12.0	>12.0
True Thyroxin (TT_4) (micrograms per 100 ml)	3.0 to 7.5	5.5 to 10.5	>10.5
Resin Triiodothyronine Uptake (RT_3) (percent)	25.0 to 35.0	<21.0	>25.0
Free Thyroxin Index (product of TT_4 multiplied by RT_3)	0.75 to 2.6	0.75 to 2.6	> 2.6
Free Thyroxin (nanograms per 100 ml)	4.5 to 8.5	3.2 to 5.6	> 8.5

pregnancy. The PBI remained elevated throughout the duration of the pregnancy, dropping back to the normal range about a month after delivery. Initially, it was suspected that there might be some thyroid dysfunction in pregnancy, although it was clear there were no other signs of thyrotoxicosis. With the discovery of thyroxin-binding globulin and the recognition of its importance in the transport of thyroxin, the PBI changes in pregnancy were clarified.

Robbins and Rall[3] in 1957 discovered in normal pregnant females the increased capacity of the serum to bind thyroxin and showed that this capacity rose early in pregnancy, remained high throughout pregnancy, and returned to normal about one or two months after delivery. It is the rise in thyroxin-binding globulin in pregnancy which is responsible for the elevated PBI. More recently, we have measured TT_4, as determined by the method of Pattee and Murphy,[4] which has the advantage that it is not interfered with by inorganic or organic iodides. The normal range for TT_4 in the nonpregnant female is 3.0 to 7.5 micrograms per 100 ml and in the pregnant female 5.5 to 10.5 micrograms per 100 ml.

The resin T_3 uptake, another commonly available thyroid function test, measures the degree of saturation of thyroxin-binding protein. In normal persons, the resin uptake is 25 to 35 percent. In the pregnant woman, the elevated level of circulating thyroxin-binding protein results in more available binding sites in the serum, so that the spillover onto the resin of the added T_3 is diminished; therefore, the T_3 uptake is depressed. The normal T_3 uptake in pregnancy is usually below 21 percent. The characteristic findings in pregnancy, then, are a high PBI, a high TT_4, and a low T_3 uptake.[5]

We have used the product of PBI multiplied by T_3 uptake, or TT_4 multiplied by T_3 uptake, to give us an index of free thyroxin (Chart 1). In pregnancy, the TT_4 is elevated, the T_3 uptake is depressed, but the product of the two still results in a normal free thyroxin index. The use of a nomagram such as Chart 1 makes this calculation quite simple. Actual measurements of free thyroxin in pregnancy reveal it to be in the same range as for the nonpregnant woman.[6]

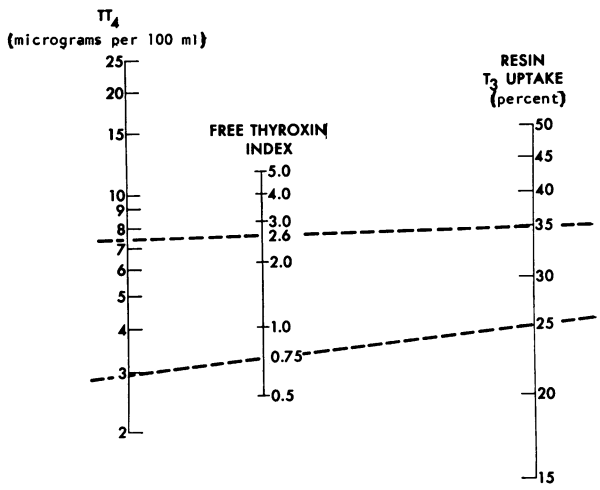

Chart 1.—Nomagram for free thyroxin index. The product of the true thyroxin iodide (TT_4, microgram per 100 ml) and the resin T_3 uptake (percent) yields the "free thyroxin index" in arbitrary units. The dotted lines indicate the range of normal values.

The diagnosis, then, of thyrotoxicosis in pregnancy is simply that there is a higher level of circulating thyroxin in the thyrotoxic pregnant woman than there is in the nonthyrotoxic pregnant woman. Therefore, in the patient with hyperthyroidism and pregnancy, the PBI is usually over 12, the TT_4 is over 10, and the T_3 uptake is usually over 25 percent (Table 1). In the patient presented today, the TT_4 was 23 micrograms per 100 ml, and the T_3 uptake was 52 percent. These values yield a free thyroxin index of about 12, which is enormously elevated.

Placental Transport

Iodide: In dealing with pregnant patients with thyrotoxicosis, we must consider the problem of

placental transport in order to evaluate the effect of the disease and proper treatment on the fetus. The placenta is considered to be freely permeable by iodide ion, but there has been a question as to when the fetal thyroid begins to function and take up iodine. This has been studied by Evans and his colleagues,[7] who administered radioiodine to women who were about to have a therapeutic abortion. He was able to demonstrate that the fetal thyroid began to accumulate iodine shortly after the third month of the pregnancy. This was indirectly confirmed by Russel and coworkers,[8] who reported two patients with thyroid cancer treated inadvertently with radioiodine at about three months of pregnancy. In both instances, the neonate was found to be decidedly hypothyroid. Although these patients received very large doses of radioiodine (75 to 225 millicuries), in general we wish to avoid the use of radioiodine after the third month of pregnancy because of the possibility of radiation damage to the fetal thyroid. Large doses of inorganic iodide have been shown to induce goiter and hypothyroidism in the fetus. In the case reported by Galina and coworkers,[9] the doses of iodide were extremely large (about 1,200 mg per day) and the infant actually died of asphyxiation from a large iodide-induced goiter. This must be an extremely rare situation, but it indicates caution in the use of large doses of iodides during pregnancy, as well as avoidance of radioiodine during pregnancy.

Propylthiouracil: Early studies on propylthiouracil in animals demonstrated that it crossed the placenta very easily and produced hypothyroidism and goiter in the pups.[10] In 1957, Krementz and coworkers[11] reported 15 infants with goiter from mothers treated with propylthiouracil during pregnancy. Although this would seem to contraindicate the use of propylthiouracil during pregnancy, the incidence of goiter in the fetus may depend directly upon the dose of propylthiouracil administered to the mother, so that a safe dose of propylthiouracil can be achieved, as I will discuss later.

Thyroxin: The transport of thyroxin across the placenta at term was studied by Grumbach and Werner[12] in 1956. They administered radioiodine labeled thyroxin to the mother shortly before delivery, blocked the gland with iodide, and then measured the maternal-fetal ratio of labeled thyroxin from appropriate blood samples. They found that the maternal-fetal blood ratio was approximately 10:1 at 7 hours, and 7:1 at 16 hours after injection, suggesting a very slow transfer of thyroxin across the placenta.

Fisher and coworkers,[13] using a slightly different technique, actually calculated the rate of transport of thyroxin across the placenta. They showed that with a dose of 2 to 4 mg administered to the mother, the transport rate was roughly 4 micrograms of T_4 per hour, and with 8 mg administered to the mother, the placental transport rate was 14 micrograms per hour. These transport rates are extremely slow.

Why does thyroxin cross the placenta so slowly? French and Van Wyk[14] suggested that this rate primarily results from the tremendous thyroxin binding capacity of maternal serum in relation to fetal serum.

The practical problem of how to get enough thyroxin into the mother to raise the fetal serum thyroxin level was approached by Carr and his colleagues[15] in 1959. They administered 20 to 24 grains of desiccated thyroid daily to two mothers who had previously borne athyreotic children. This is a very large dose, about ten times the normal adult requirement of desiccated thyroid. With this large dose, however, they were able to demonstrate normal development in one child who was later shown to be athyreotic. The important point about this study is that in order to achieve normal serum thyroxin levels in the fetus, one must administer very large doses of thyroxin or thyroid hormone to the mother. T_3 also crosses the placenta quite slowly, so that there is no real advantage to treating mothers with this material in an effort to achieve euthyroidism in an athyreotic fetus.[16]

TSH and LATS

Anterior pituitary thyrotropic hormone (TSH) does not cross the placenta. The long-acting thyroid stimulator (LATS), an immune gamma globulin, crosses the placenta very well. Indeed, the active placental transport of LATS is probably the cause of neonatal Graves' disease. In this syndrome, the mother is or was hyperthyroid and usually has exophthalmos or recurrent Graves' disease. The child is born with periorbital edema, slight exophthalmos, goiter, tachycardia, fever, and a very skinny appearance; and the TT_4 and T_3 uptakes are decidedly elevated. Treatment usually involves supportive therapy with food and fluids, plus the administration of iodides and propylthiouracil. The child spontaneously recovers in about

TABLE 2.—*Management of Thyrotoxicosis in Pregnancy*

Treatment	Pregnancies (number)	Maternal Mortality (percent)	Fetal Mortality (percent)	Fetal Abnormalities (number)	Reference
Supportive	31	0	45	0	18
Potassium iodide, surgery	41	0	4	0	19
Propylthiouracil, iodide, surgery	21	0	24	0	20
Mercaptoimidazole, iodide, surgery, with or without T_4 postoperatively	21	0	5	0	20
Propylthiouracil, iodide, surgery	38	0	5	0	21
Propylthiouracil	19	0	0	0	22
Propyl- or methylthiouracil or mercaptoimidazole, terminated antepartum	16	0	31	1	23
Propylthiouracil, T_4	27	0	7.5	1	24
Propylthiouracil, T_4	32	0	9	0	25

a month, usually with no residua. McKenzie[17] has shown high levels of LATS in both mother and child, with a gradual disappearance of the LATS level in the infant. The half-life of LATS is about one or two weeks. These observations are a strong argument in favor of the concept that LATS, or an antibody similar to it, is actually an etiological factor in the development of Graves' disease.

In summary, then, we recognize that iodide and propylthiouracil cross the placenta very easily, thyroxin and T_3 cross very slowly and against a gradient, and TSH does not cross the placenta at all. LATS, like other small antibodies, is transported across the placenta quite well and may actually cause disease in the infant.

Management

A series of reports concerning the management of thyrotoxicosis in pregnancy is summarized in Table 2. In 1929, Gardiner-Hill[18] reported a group of patients who were pregnant and thyrotoxic and who were carried through pregnancy with only supportive therapy. The maternal mortality was zero, but the fetal mortality was 45 percent (including abortions, stillbirths, and premature infants who died very shortly after birth). Mussey and Plummer[19] in 1931 reported a group of 41 patients who were treated with potassium iodide and surgical operation, and fetal mortality was only 4 percent. In 1960, Bell and Hall[20] reported a group of patients who were treated with propylthiouracil and iodide, and then subtotal thyroidectomy. The fetal mortality was somewhat higher, about 24 percent. He noted that many of these patients became hypothyroid postoperatively. Therefore, he treated the next group of patients with thyroxin postoperatively and found that the fetal mortality dropped considerably. A later study with comparable therapy again revealed a fetal mortality of about 5 percent.[21] These data indicate that operation preceded by propylthiouracil therapy and including postoperative thyroxin treatment to the mother is a very satisfactory way of handling this problem.

On the other hand, the use of propylthiouracil alone is also quite satisfactory. Therapy of this type was first reported by Astwood[22] in 1951. He treated 19 patients with no incidence of fetal or maternal mortality. He used propylthiouracil in initial doses of around 300 mg and reduced the dose as the disease improved. Later workers were not quite so careful. Piper[23] in 1954 treated patients with methyl- or propylthiouracil in doses of 400 to 500 mg daily. He stopped the medication two months before delivery. With this procedure, fetal mortality was about 31 percent. Asper[24] and Herbst[25] used propylthiouracil in addition to thyroxin. They administered 300 mg of propylthiouracil initially, then reduced the dose and added thyroxin in doses of 0.2 to 0.4 mg daily. Their overall fetal mortality was 7.5 to 9 percent. As I have already pointed out, thyroxin does not cross the placenta in significant quantities, and since the goal in therapy is to reduce the dose of propylthiouracil to the minimum required to maintain the mother euthyroid, the addition of thyroxin is really quite unncessary. If the patient can be controlled on doses of 300 mg or propylthiouracil (in divided doses) initially, with maintenance doses of 100 to 150 mg daily, the likelihood of fetal hypothyroidism is extremely small.

In summary, we have two good methods for the management of thyrotoxicosis in pregnancy. The first is preparation with propylthiouracil and iodide and subtotal thyroidectomy in the middle trimester of pregnancy. This regimen is associated with a very low maternal mortality and, provided the patient receives supplemental thyroxin during the latter part of pregnancy, the fetal mortality is also very low. As a second method the patient can be treated with propylthiouracil alone, keeping

the dosage down to the minimum which will keep the mother euthyroid.

In the particular patient under discussion today, the decision was made to prepare her for subtotal thyroidectomy in the middle trimester of pregnancy. I think this will be a very effective and satisfactory form of therapy.

DR. SMITH: Thank you very much, Dr. Greenspan. Are there any questions or comments?

DR. HAVEL:* Will you comment on fetal abnormalities when propylthiouracil is given at the time of conception?

DR. GREENSPAN: I do not think there are any data. There are reports of a fairly large number of patients who became pregnant while taking propylthiouracil. They were euthyroid and were carried through the pregnancy on small doses of the drug without evidence of fetal abnormality. The major problem one gets into is abortion, uncontrolled disease, or goiter in the child if the dosage of propylthiouracil is too high for too long. We have not really seen evidence of other congenital malformations in newborns when the mothers were treated with relatively low doses of propylthiouracil throughout pregnancy.

QUESTION: Would propranolol alone be useful in management of thyrotoxicosis in pregnancy?

DR. GREENSPAN: I have had no experience with propranolol used alone. We have in general felt that it was extremely important to bring the level of circulating thyroxin down by appropriate antithyroid drugs. Propranolol has been used very effectively in management of thyrotoxic storms, which may occur in a patient who is untreated and goes through labor, but I have had no experience with its use alone.

*Richard J. Havel, M.D., Associate Director, Cardiovascular Research Institute, and Professor of Medicine.

REFERENCES

1. Becker WF, Sudduth PG: Hyperthyroidism and pregnancy. Ann Surg 149:867, 1959
2. Man EB, Heinemann M, Johnson CE, et al: Precipitable iodine of serum in normal pregnancy and its relation to abortions. J Clin Invest 30:137, 1951
3. Robbins J, Rall JE: Interaction of thyroid hormones and protein in biological fluids. Rec Prog Hormone Res 13:161, 1957
4. Murphy BEP, Pattee CJ, Gold A: Clinical evaluation of a new method for the determination of serum thyroxine. J Clin Endocrin Metab 26:247, 1966
5. Clark F: Letter to the editor. Lancet 2:167, 1963
6. Sterling K, Hegedus A: Measurement of free thyroxine concentration in human serum. J Clin Invest 41:1031, 1962
7. Evans TC, Kretzschmar RM, Hodges RE, et al: Radioiodine uptake studies of the human fetal thyroid. J Nucl Med 8:157, 1967
8. Russel KP, Rose H, Starr P: Effects of radioactive iodine on maternal and fetal thyroid function during pregnancy. Surg Gyn Obstet 104:560, 1957
9. Galina MP, Avnet NL, Einhorn A: Iodides during pregnancy. New Eng J Med 267:1124, 1962
10. Freiesleben E, Kjerulf-Jensen K: Effect of thiouracil derivatives on fetuses and infants. J Clin Endocrin Metab 7:47, 1947
11. Krementz ET, Hooper RG, Kempson RL: Effect on the rabbit fetus of the maternal administration of propylthiouracil. Surgery 41: 619, 1957
12. Grumbach MM, Werner SC: Transfer of thyroid hormone across the human placenta at term. J Clin Endocrin Metab 16:1392, 1956
13. Fisher DA, Lehman H, Lackey C: Placental transport of thyroxine. J Clin Endocrin Metab 24:393, 1964
14. French FS, Van Wyk JJ: Fetal hypothyroidism. J Pediat 64: 589, 1964
15. Carr EC, Bierwaltes WH, Ramand G, et al: Effect of maternal thyroid function in fetal thyroid function and development. J Clin Endocrin Metab 19:1, 1959
16. Osorio C, Myant NB: Passage of thyroid hormone from mother to foetus and its relation to foetal development. Brit Med Bull 16:159, 1960
17. McKenzie JM: Neonatal Graves' disease. J Clin Endocrin Metab 24:660, 1964
18. Gardiner-Hill H: Pregnancy complicating simple goitre and Graves' disease. Lancet 1:120, 1929
19. Mussey RD, Plummer WA: Treatment of goiter complicating pregnancy. JAMA 97:602, 1931
20. Bell GO, Hall J: Hyperthyroidism and pregnancy. Med Clin N Amer 44:363, 1960
21. Hawe P: The management of thyrotoxicosis during pregnancy. Brit J Surg 52:731, 1965
22. Astwood EB: Use of antithyroid drugs during pregnancy. J Clin Endocrin Metab 11:1045, 1951
23. Piper J, Rosen J: Management of hyperthyroidism during pregnancy. Acta Med Scand 150:215, 1954
24. Asper SP, London F: Thyrotoxicosis and pregnancy. Amer Climatol Assoc 72:110, 1960
25. Herbst AL, Selenkow HA: Hyperthyroidism during pregnancy. New Eng J Med 273:627, 1965